EVALUATION OF PHARMACEUTICAL CREAM PRODUCTION DEBOTTLENECKING SCHEMES

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Abstract: The main objective of this work is to model and debottleneck a pharmaceutical production of an anti-allergic cream. The base case process has a minimum cycle time of 29 hours which is equivalent to 66 batches/year. Four schemes were proposed for process debottlenecking due to the anticipated increase of the product demand of 150% in the market. By carrying out throughput analysis study, schemes that fulfil the debottlenecking objective were determined. Out of the four debottlenecking schemes, Scheme 4 was chosen, which proposed a new blending tank and intermediate tank, showed a production increase of over 150%.

Keywords: Batch, modelling, optimisation, throughput, scheduling.

1. INTRODUCTION

Computer Aided Process Design (CAPD) and simulation tools have been widely used in the bulk and petrochemical industries since the early 1960's. It involves the use of computers to perform steady-state heat and mass balancing as well as sizing and costing calculations for a process (Westerberg *et al.*, 1979). However, the use of these CAPD and simulation tools has only emerged in the pharmaceutical manufacturing in the past decade (Petrides, *et al.*, 1995; Hwang, 1997; Ernst, *et al.*, 1997; Koulouris, *et al.*, 2000; Petrides, *et al.*, 2002a, b; Oh, *et al.*, 2004). Compared to the readily available commercial process simulators in the bulk and petrochemical industries, there are only a limited number of commercial simulators available for pharmaceutical process modelling in the market, which include Batches by Batch Process Technologies, Batch Plus by Aspen Technology, SuperPro Designer by Intelligen as well as Batch Design Kit by Hyprotech. This situation is mainly due to the constraints associated with the modelling of pharmaceutical processes, which include the uncommon unit operations and batch operation nature of pharmaceutical processing. Due to its relatively new emergence, much work needs to be done in this sector.

This paper describes the use of the commercial batch process simulator SuperPro Designer v5.0 in the modelling and debottlenecking of an anti-allergic cream production line at a local pharmaceutical facility. Due to the increasing customer demand of the anti-allergic cream product, the pharmaceutical facility management team is looking for alternative expansion schemes to increase the current production rate as the production capacity is limited by the current operating condition and equipment setup. Hence, a debottlenecking study is needed for an increase in production.

2. BACKGROUND THEORY

In order to increase the process throughput the process bottleneck that limits the current production need to be identified. Bottlenecks are process limitations that are related to either equipment or resource such as demand for various utilities, labour, raw material, etc. Hence, process debottlenecking can be defined as the identification and removal of obstacles in the attempt to increase the plant throughput (Koulouris, *et al.*, 2000). In batch manufacturing, two types of process bottlenecks can be categorised. These are the equipment capacity-

related size bottleneck (an equipment that is limited in size) as well as the scheduling bottleneck (due to the long occupancy of an equipment during a process). The ability to identify and remove process bottlenecks that create obstacles in a manufacturing process will increase plant throughput and fulfil customer needs.

A good tool to identify batch process bottleneck is via a throughput analysis study. Throughput analysis measures the equipment utilisation in a batch process with two variables, i.e. the capacity utilisation and equipment uptime (Koulouris, *et al.*, 2000; Petrides, *et al.*, 2002a). Capacity utilisation is defined as the percentage of the current operating load of an equipment relative to its maximum load. On the other hand, equipment uptime measures the effectiveness of a piece of equipment that is utilised in time. It is given as the percentage of the equipment utilisation time over the plant cycle time. The product of equipment capacity utilisation and its uptime defines the combined utilisation of the respective equipment (Koulouris, *et al.*, 2000; Petrides, *et al.*, 2002a). The processing step with the highest combined utilisation is identified as the process bottleneck. Simulation tools that are capable of tracking capacity utilisation and equipment uptime can facilitate the identification of process bottlenecks and the development of the scenarios for process debottlenecking. By using the "what if" scenario, process alternatives can be simulated via the use of simulation tools to reveal potential candidates for the debottlenecking study.

3. MODEL DEVELOPMENT

Fig. 1 shows the base case simulation flowsheet for the production of anti-allergic cream modelled in SuperPro Designer v5.0. Due to the nature of the process that is operated in batch mode, the base case simulation model was developed to reflect the actual operating condition of the current production in the existing pharmaceutical manufacturing facility.

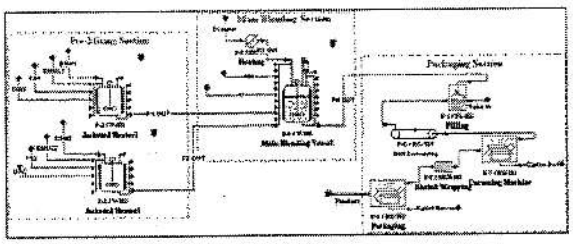

Fig. 1. Base case simulation flowsheet for the production of anti-allergic cream.

In the base case process, there are nine major processing steps in three different sub-sections. This includes raw material melting in the Pre-mixing Section, Main Blending Section, as well as filling, cartoning, packaging (shrink wrapping) and shipment packaging in the Packaging sections. Fifty two operation weeks were taken as the basis of this work. Two batches of emulsifying wax (ESW) and foam stabiliser (FS) are independently heated in the heating procedures P-1 (carried out in Jacketed Heater V-101) and P-2 (in Jacketed Heater V-102) to approximately 100°C before the emulsifier (EMUL) and ointment (OIN) are added.

Deionised (DI) water is heated in the electric heater EH-101 (procedure P-3) before being transferred into the Main Blending Tank, V-103 (P-4) in the Main Blending Section. An antimicrobial agent (AM) is next added into the hot DI water. The mixture in the jacketed heater V-101 and V-102 is then transferred into V-103 and all ingredients in V-103 are blended for a uniform composition. The mixture is then left in an air-conditioned dispensing room to be naturally cooled to room temperature. This cooling operation took approximately 19 hours to accomplish due to the slow rate of natural cooling. Upon the completion of the cooling operation, the active ingredient (AI) of the anti-allergic cream is finally added before the product mixture is sent to the Packaging Section.

In the Packaging Section, the anti allergic cream is filled into the tubes of 15 g each. The existing filling machine is operated at a speed of 30 tubes/min. The tubes are then sent to the cartoning packaging procedure P-7 (using a belt conveyer P-6/BC-101) where the anti-allergic cream in tubes are packed manually by two operators into the tube cartons, each at a speed of 20 cartons/min. Next, 12 cartons of anti-allergic cream are packed into one wrapper in the shrink wrapper (P-8/GBX-101), with a speed of 5 wrapper/min. Finally, 6 wrappers are packed into each of the pallet boxes in P-9/BX-102 (equivalent to 72 tubes/pallet box) before they are sent to the warehouse. Approximately 6 sealed pallet boxes are packed per minute by the operator manually.

As the manufacturing process is carried out in a batch operation, efforts have been made to document the scheduling details of each processing steps. The Operation Gantt Chart for the complete recipe of a single batch operation is shown in Fig. 2. It should also be noted that the process time for certain operations are dependant upon other operations of other procedure (e.g. Transfer-out function in P-4 is set equal to the filling duration of P-5). Hence, the duration of this slave operation is set to follow to the duration of the master operation using the Master-Slave Relationship function of SuperPro Designer (Intelligen, 2003).

The customer demand for this anti-allergic cream product is expected to rise another 150% of the current production capacity in coming years. However, the process is currently running at its maximum capacity and any attempt of increasing production is not possible due to the process bottleneck. This calls for a systematic procedure to analyse the current production facilities and next, to debottleneck the process.

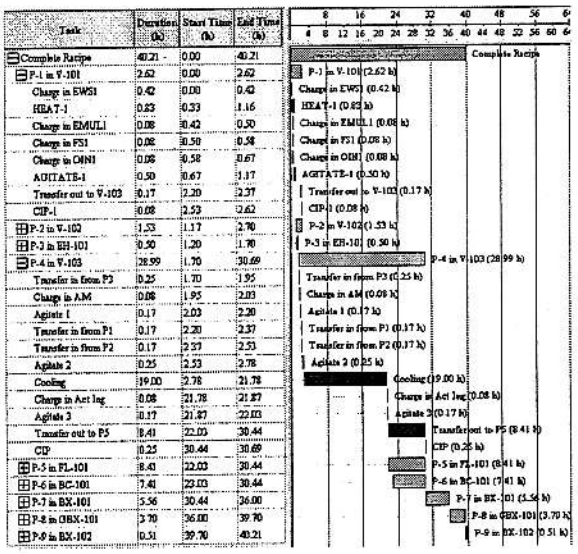

Fig. 2. Operation Gantt Chart for the base case simulation.

4. BOTTLENECK IDENTIFICATION STRATEGIES

From the base case simulation, a complete batch of pharmaceutical cream production has a process batch time of 40.2 hrs and a minimum cycle time of 29 hrs. The minimum cycle time of the process sets the plant annual production at 66 batches, with 13,333 tubes of anti-allergic cream produced per batch. The capacity, time and combined utilisation of all the procedure/equipment pairs in the base case simulation. As shown in Fig. 3, the Main Blending Procedure P-4 (V-103) has the highest combined utilisation of all procedures. The product of equipment utilisation and uptime leads to the highest combined utilisation of 84.1% for P-4/V-103, and hence it is identified as the overall process bottleneck. After identifying the Main Blending Procedure P-4 (V-103) as the process bottleneck, debottlenecking strategies will next be focused on reducing either the size or time utilisation of this procedure/equipment.

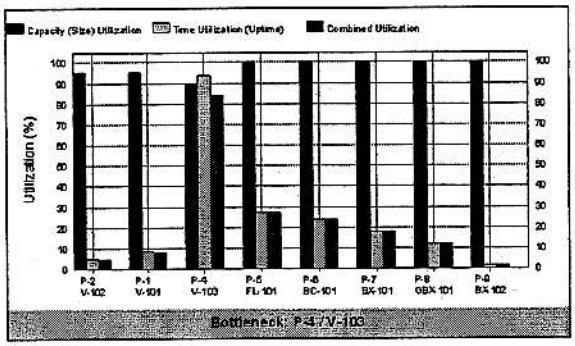

Fig. 3. Capacity, time and combined utilisation for unit procedures in base case simulation.

5. DEBOTTLENECKING SCHEMES

After identifying the candidate for process debottlenecking, the feasibility of various debottlenecking schemes were evaluated using SuperPro Designer. Four debottlenecking schemes were analysed in which all schemes were applied focusing on reducing the equipment uptime of P-4/V-103 as the process time bottleneck.

For debottlenecking Scheme 1, a new intermediate tank V-104 is installed after the Main Blending vessel. The Transfer-out operation in P-4/V-103 is no longer constrained by the slow filling operation in Filler P-5/FL-101. Upon the completion on the blending operations in P-4/V-103, the product mixture is transferred into the newly added V-104 for temporary storage, while waiting for the filling operation to complete. Simulation results showed that the annual production for this scheme is determined as 87 batches, with the reduction of minimum cycle time that limits the number of annual production from 29 hrs (in the base case simulation) to 21.6 hrs. This corresponds to an increase of annual production rate of 32%, but is insufficient to fulfil projected customer demands.

Scheme 2 focuses on the reduction of cooling operation of P-4/V-103 instead. A multifunctional blending tank with a cooling system (purchase cost of USD 255,000) is installed to replace the main blending tank. This reduces the cooling time of the product mixture from the current 19 hours to 5 hours. Chilled water is used as cooling agent to cool the mixture from 85°C to room temperature. This leads to the reduction of minimum cycle time to 15 hrs. Hence, an increase of 83.3% is achieved for annual production as compared to the base case, i.e. from 66 to 121 batches. However, P-4/V-103 remains as the overall process bottleneck although its combined utilisation value has been reduced from the current 84.2% to 79.3% (as the uptime was reduced from 94% to 88%). Further debottlenecking can only be achieved if the long duration of its Transfer-out operation (to filler P-5/FL-101) can be reduced.

Scheme 3 explored the reduction of P-4/V-103 uptime from a different perspective where a new filler (50 tubes/min; purchase cost of USD 300,000) is installed in addition to the new multifunctional blending tank in Scheme 2 to accelerate the filling rate. An annual production of 147 batches with a minimum cycle time of 12 hrs is achieved. Simulation results showed that, although the duration of Transfer-out operation in P-4/V-103 can be reduced significantly, the combined utilisation value of P-4/V-103 is only reduced slightly to 77.10% (from 79.34%) in Scheme 2). The resulting annual production is determined as 147 batches, i.e. an increase of 122.7%.

Another debottlenecking alternative focusing on reducing the overall uptime of P-4/V-103 is presented

in Scheme 4 (Fig. 4). Instead of installing a new filling machine as in Scheme 3, an intermediate storage tank (V-104; purchase cost of USD10,000) is added here in addition to the installation of a new Blending Tank (P-4/V-103). Simulation results showed that the annual production for this scheme is 173 batches with a minimum cycle time reduced to 9.9 hrs. This corresponds to an increase of annual production rate of 162%, fulfilling the future market demand.

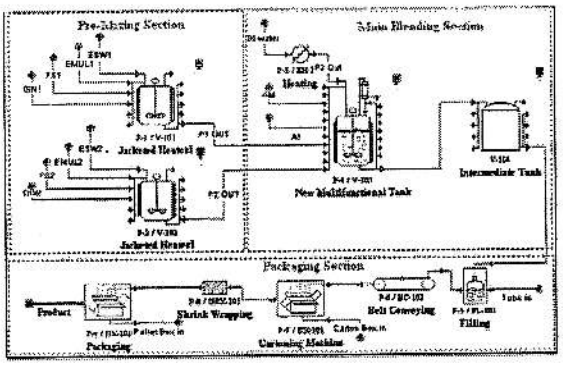

Fig. 4. Debottlenecking Scheme 4 with the installation of intermediate tank and new multifunctional blending tank.

It should also be noted that after the installation of intermediate storage tank P-10/V-101, the main blending tank (P-4/V-103) is no longer the process bottleneck. This is consistent with the finding of Koulouris *et al.* (2000), where new bottleneck equipment will emerge after the current bottleneck is overcome. Debottlenecking efforts are stopped at this scheme as the debottlenecking objective is reached, i.e. achieving the 150% increase in production as compared to current production.

6. CONCLUSION

In this work, computer-aided process design (CAPD) and simulation tools are used in the systematic identification of the process bottleneck and a debottlenecking study. A local pharmaceutical case study of anti-allergic cream production is used to demonstrate the effectiveness of the tools. The base case and four debottlenecking schemes are simulated using SuperPro Designer. It is shown that with the reduction of equipment uptime of the process time bottleneck, the annual process throughput is increased significantly. The study resulted in a debottlenecking scheme that achieves the current production needs.

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